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(71) Applicant: **BIOFARMITALIA S.p.A.**

20144 Milano (IT)

(72) Inventors:

- **Pinna, Marco**
21051, ARCINATE (VA) (IT)
- **Pinna, Fausto**
20050, LESMO (MI) (IT)

(74) Representative: **Frignoli, Luigi**

**Giambrocono & C. s.p.a.,
Via Rosolino Pilo, 19/B
20129 Milano (IT)**

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(54) **Patch containing a substance selected from tars having reducing characteristics in dermatology**

(57) A patch consisting of a porous or occlusive woven, non-woven or plastic support, to one face of which is applied a skin adhesive polymer layer containing tars used as reducers or resolvents in dermatology, in partic-

ular ichthyol, able to gradually release the active substances in order to maximize their therapeutic properties.

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Description

[0001] The present invention provides a transpirable or non-transpirable patch or the like, one surface of which is at least partially covered by a skin-adhesive polymer layer able to retain sufficient doses of tars used as reducers or resolvers in dermatology, such as ichthyol or sulfonated ichthyol, and to suitably release their therapeutically active substances.

[0002] Tars used as reducers in dermatology are classically divided into: vegetable tars, bituminous tars such as ichthyol and ichthammol, and tars from fossil coal (coal tar). Currently, vegetable tars are little prescribed because application methods used up to now can give rise to irritation, and are hence applied only to poorly sensitive skin for just a few days, so avoiding treatment of irritable areas. Ichthyol and ichthammol have been progressively abandoned as they are often sensitizing and difficult to use. Ichthyol is a product derived from the dry distillation of an oil shale and has similar characteristics to coal tar, it containing 10% of sulphur.

[0003] It has long been used for its anti-inflammatory, antiseptic, vasoconstricting and anti-pruritic action. It is soluble in water and is therefore often formulated as aqueous preparations for psoriasis of the face, for atopic dermatitis and acne. The odour of sulphur-containing preparations is very strong and unpleasant. Applying the ointment is difficult and uncomfortable as it is stringy. After use the area has to be washed to remove residues and any stains left on the skin following treatment. The posology required for these cutaneous manifestations is several applications during the day. In frequent cases ichthyol is used to clear up anal fistulas by applications of ointments, creams or gauzes impregnated with ichthyol based solutions which stain, dirty and irritate all the surrounding area and the underwear, to the extent of seeping onto the outer clothing with its evident complications. Moreover once the abscess has matured, the discharge of mucopurulent material, because it is not retained, spreads out and compromises the entire area.

[0004] Ichthyol can give rise to irritation and sensitivity if applied to particularly delicate areas, hence it is important to have a pharmaceutical form, such as a patch, which can ensure a constant release of the active substance, but without ever reaching a concentration such as to be poorly tolerated by the skin.

[0005] The main object of the present invention is to provide a patch, one surface of which carries a polymer layer applicable to human skin by virtue of its adhesiveness containing sufficient doses of ichthyol or ichthyol sulfonate or tumenol, coal tar or another tar used as a reducer in dermatology, which is able to treat the specific afflicted area with a limited quantity of substance, without invading the surrounding areas so as to avoid intolerances and sensitizations, is able to release the substance in a gradual and constant manner with time, and is able to retain and absorb the mucopurulent material which escapes after the pimple, fistula or abscess has cleared up.

[0006] These objects are achieved by a patch characterized by a layer of skin-adhesive polymer applied to one of its faces, which contains at least one substance chosen from tars used as reducers in dermatology with cosmetic or therapeutic activity, and consisting more specifically of a flexible support of non-woven fabric, cotton or another fabric or plastic material, to at least one surface of which a layer of adhesive polymer is applied, chosen from synthetic groups, for example acrylic in a water or solvent base, vinyl in a water or solvent base, polyurethane, resins of natural or synthetic origin, polyacrylates, or natural polymers such as gums, polyvinyl alcohols, cellulose, carrageenan, alginates, etc. within which polymer a substance is dispersed chosen from tars used as reducers or resolvers in dermatology in a percentage variable between 0.1 and 60% of its final weight on the patch, with the possible addition of between 0% and 10% of a substance of vegetable origin comprising essential oils and aromatic extracts; and between 0% and 10% of a skin-compatible component chosen from the group comprising soothing substances, skin repairers, cicatrizants, anti-inflammatories, antiseptics and bactericides, the percentages being by weight.

[0007] The polymer can also contain between 0.0% and 5% by weight of a useful but non-essential compound chosen from the group formed from wetting solvents, preservatives, emulsifiers, stabilizers, solubilizers, surfactants and colorants.

[0008] Within the patch the polymer is preferably present in a quantity from 70% to 97% by weight, the substance selected from tars used as reducers, preferably pure or sulfonated ichthyol or tumenol being between 1% and 30% by weight, soothing substances, skin repairers, cicatrizants, anti-inflammatory, antiseptic or bactericide being between 0% and 5%, and between 0.0% and 2% by weight of a component chosen from the group formed from wetting solvents, preservatives, emulsifiers, stabilizers, solubilizers, surfactants and colorants, the percentages being by weight.

[0009] The preferred polymers are chosen from the group comprising acrylic, polyacrylic, polyurethanic polymers, synthetic or natural resins, polyvinyl alcohol, sodium alginate, calcium alginate, carboxymethylcellulose, sodium polyacrylate and polyvinylpyrrolidone.

[0010] Some non-limiting embodiments are described hereinafter to further clarify the understanding of the nature, shape and structure and of the method of obtaining the patch.

EXAMPLE 1

Preparation of an ichthyol based patch for treating anal fistulas

[0011] 8.7 kg of a non-crosslinked solvent acrylic adhesive (for example Duro-tak 387-2353 adhesive by National Starch & Chemical) and 323 grams of pure ichthyol are introduced into a container under cold conditions and

mixed with a propeller stirrer until a uniform mass is obtained. The mass is left to stand to enable any air bubbles to escape. Using a patch spreading machine and with the aid of a compressed air pump, the mixture is fed into the rotating roller doctor blade with the doctor blade thickness adjusted to about 300 micron. The mixture is filmed onto a siliconized polyester which passes through 4 oven stations, the first set at 40°C, the second at 50°C, the third at 70°C and the fourth at 80°C, at a rate of 8 metres per minute. At the oven exit the film is completely free of solvents, which have evaporated within the oven stations, the body of the adhesive mass is blackish in colour showing the presence of 10% pure ichthyol, the weight of the adhesive mass being about 90 grams per square metre. The polyester on which the adhesive film was spread and dried is bonded to a polyester and viscose non-woven fabric of 100 grams per square metre and rewound onto a bobbin. The result is that the adhesive film grips the non-woven fabric to form an adhesive fabric containing 10% ichthyol protected by the siliconized polyester. Round patches of 4 centimetres diameter are then punched from the obtained bobbin and packaged. These patches were tested by HPLC to verify the quantity of pure ichthyol present, in each patch a quantity of 11.3 mg of ichthyol being found, equal to 10% of the total adhesive mass.

[0012] Tests subsequently undertaken by organized clinical structures on persons with anorectal fistulas or abscesses demonstrated the absolute effectiveness of the product. The abscess was found to re-absorb with complete resolution of pain and tissue symptomology. In the space of 8-10 hours there is a progressive recession of characteristic symptoms: anoperineal pain and swelling, irritation and reddening of the perineal skin (itching, burning, and pus).

EXAMPLE 2

Preparation of an ichthyol based patch for treating anal fistulas.

[0013] 20 kg of a crosslinked solvent acrylic adhesive with average viscosity 2500/3000 mPa.s (for example Duro-tak 387-2054 adhesive by National Starch and Chemical) and 5 kg of solvent acrylic adhesive with 700-800 mPa.s low viscosity were introduced under cold conditions into a container then mixed slowly for 20 minutes with a vertical agitator. While slowly agitating, 2100 grams of pure ichthyol (ammonium sulfoichthyolate), 247 g of tumenol and 123 grams of fluid Aloe Vera extract are introduced as a thin stream. Mixing continues slowly until a uniform mass is obtained then left to stand to release any air bubbles. Using a patch spreading machine and with the aid of a compressed air pump, the mixture is fed into the rotating roller doctor blade with the doctor blade thickness adjusted to about 320 micron. The mixture is filmed onto a siliconized polyester which passes through 4 oven stations, the first set at 40°C, the second

at 50°C, the third at 80°C and the fourth at 90°C, at a rate of 8 metres per minute. At the oven exit the film is completely free of solvents, which have evaporated within the oven stations, the body of the adhesive mass is blackish in colour showing the presence of 8% pure ichthyol, 1% tumenol, 0.5% Aloe Vera, the weight of the adhesive mass being about 100 grams per square metre. The polyester on which the adhesive film has been spread and dried is bonded to a micro-perforated corona treated polythene film of 90 g/m² and rewound on a bobbin. The result is that the adhesive film grips the micro-perforated polythene to form an adhesive fabric containing 8% ichthyol, 1% tumenol and 0.5% Aloe Vera protected by the siliconized polyester. Round patches of 4 centimetres diameter are then punched from the obtained bobbin and packaged.

[0014] These patches were tested by HPLC to verify the quantity of pure ichthyol present, in each patch a quantity of 8.9 mg of ichthyol being found, equal to 8% of the total adhesive mass.

EXAMPLE 3

Preparation of an ichthyol based patch for treating inflammatory changes of the skin.

[0015] 28 kg of demineralised water, 0.120 kg of parabens (preservatives), 4.4 kg of polyvinyl alcohol and 0.5 kg of carboxymethyl cellulose are introduced into a mixer heated to 70°C to obtain a uniform mass (Phase A) which is cooled to ambient temperature and then poured into a kneader into which Phase C, formed of 3 kg of ichthyol (ammonium sulfoichthyol), 2.0 kg of carboxymethyl beta-glucan (having cicatrising action), and 18 kg of sodium alginate are added under cold conditions (over a period of about 15-20 minutes). The mixture is agitated in both directions for 15-20 minutes, after which a Phase B, prepared separately by mixing 1.8 kg of demineralised water and 0.5 kg of sodium tetraborate in a steel container at a temperature of 20-30°C until completely dissolved, is slowly added in a thin stream to give a gel whose viscosity can be increased by increasing the quantity of Phase B or decreased by increasing the quantity of Phase A.

[0016] The gel is spread by means of a rotating two roller doctor blade onto a web of non-woven fabric formed from viscose fibres (50%) and polypropylene fibres (50%), with a weight of 150 g/m², a thickness of 200 micron and a density of 87 g/dm³.

[0017] The protection sheet is a 75 g/m² siliconized polyester sheet. The composite web which leaves the rollers is transported to a machine where it is cut and punched, for example into the form of a 10 x 15 cm rectangular patch saturated throughout.

[0018] The patch thus obtained is found to be particularly effective for applications in very irritated areas, in that the refreshing action of the gel offers an immediate soothing and calming effect, the therapeutic action being

attributable to the ichthyol and to the skin repairing activity (mainly due to the carboxymethyl beta-glucan).

EXAMPLE 4

Preparation of an ichthyol based patch for treating anal fistulas.

[0019] 6 kg of a styrene and isopropene based copolymer (for example KRATON D-1161 N by Shell Chemicals), 2 kg of an alpha pinene terpene resin (for example DERCOLYTE A 115 by DRT), 10 kg of toluene and 4 kg of MEK are introduced into a container and mixed slowly for 20 minutes with a vertical agitator. 500 grams of pure ichthyol (ammonium sulfoichthyol) are added as a thin stream under slow agitation. Mixing is continued slowly until a uniform mass is obtained. The mass is left to stand to release any air bubbles. Using a patch spreading machine and with the aid of a compressed air pump, the mixture is fed into the rotating roller doctor blade with the doctor blade thickness adjusted to about 320 micron. The mixture is filmed onto a siliconized polyester which passes through 4 oven stations, the first set at 40°C, the second at 50°C, the third at 80°C and the fourth at 90°C, at a rate of 8 metres per minute. At the oven exit the film is completely free of solvents, which have evaporated within the oven stations, the body of the adhesive mass is blackish in colour showing the presence of 10% pure ichthyol, the weight of the adhesive mass being about 100 grams per square metre. The polyester on which the adhesive film was spread and dried is bonded to pure viscose non-woven fabric of 100 g/m² and rewound on a bobbin. The result is that the adhesive film grips the unwoven fabric to form an adhesive fabric containing 10% ichthyol protected by the siliconized polyester. Round patches of 4 centimetres diameter are punched from the bobbin obtained and packaged

[0020] These patches were tested by HPLC to verify the quantity of pure ichthyol present, in each patch a quantity of 7 mg of ichthyol being found, equal to 10% of the total adhesive mass.

Claims

1. Preparation of an ichthyol based patch, **characterised by** consisting of mixing 96.4% b.w. of a non-crosslinked acrylic adhesive and 3.6% b.w. of pure ichthyol in a container under cold conditions until a uniform mass is obtained, leaving the mass to stand to enable any air bubbles to escape, filming the mass onto a siliconized polyester and heating it until it is completely free of solvents, then bonding the siliconized polyester on which the adhesive film was spread to a polyester and viscose non-woven fabric so that the adhesive film grips the non-woven fabric.

2. Ichthyol based patch containing a mixture applied

on a polyester and viscose non-woven fabric, **characterised in that** said mixture includes 90% b.w. of non-crosslinked acrylic adhesive completely free of solvents and 10% b.w. of ichthyol.

3. Preparation of an ichthyol based patch, **characterised by** comprising the steps of mixing 72.8% b.w. of a crosslinked acrylic adhesive with viscosity 2500/3000 mPa.s and 18.2% b.w. of solvent acrylic adhesive with 700-800 mPa.s viscosity under cold conditions for 20 minutes, introducing as a thin stream 7.6% b.w. of pure ichthyol, 0.9% b.w. of tumenol and 0.5% b.w. of fluid Aloe Vera extract while agitating, mixing until a uniform mass is obtained, then leaving the mass to stand to release any air bubbles, filming the mixture onto a siliconized polyester which is heated until it is completely free of solvents, bonding the mass to a micro-perforated corona treated polythene film.

4. Ichthyol based patch, **characterised by** consisting of a crosslinked acrylic adhesive completely free of solvents containing 8% b.w. pure ichthyol, 1% b.w. tumenol, 0.5% b.w. Aloe Vera bonded to a micro-perforated corona treated polythene film.

5. Preparation of an ichthyol based patch, **characterised by** comprising the steps of preparing a first component by mixing together 84.8% of demineralised water, 0.4% of parabens, 13.3% of polyvinyl alcohol and 1.5% of carboxymethyl cellulose, heating the first component to 70°C to obtain a uniform mass which is cooled to ambient temperature, preparing a second component by mixing together 13.0% of ichthyol, 8.7% of carboxymethyl beta-glucan, and 78.3% of sodium alginate under cold conditions, preparing a mixture by pouring into a kneader the first and the second component and agitating for 15-20 minutes, preparing a third component separately by mixing 78.3% of demineralised water and 21.7% of sodium tetraborate at a temperature of 20-30°C until completely dissolved, all the percentages being b.w., slowly adding in a thin stream the third component to the mixture to give a gel, spreading the gel onto a web of non-woven fabric formed from 50% b.w. viscose fibres and 50% b.w. polypropylene fibres.

6. Ichthyol based patch, **characterised by** comprising 51.1% b.w. of demineralised water, 0.2% b.w. of parabens, 7.5% b.w. of polyvinyl alcohol and 0.9% b.w. of carboxymethyl cellulose, 5.1% b.w. of ichthyol, 3.4% b.w. of carboxymethyl beta-glucan, and 30.9% b.w. of sodium alginate and 0.9 % b.w. of sodium tetraborate spread onto a web of non-woven fabric formed from 50% b.w. viscose fibres and 50% b.w. polypropylene fibres.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 07 11 8333

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 01/02479 A (THE PROCTER & GAMBLE COMPANY; DECKNER, GEORGE, ENDEL; JENKINS, DELYTH,) 11 January 2001 (2001-01-11) * page 1, line 6 - line 7 * * page 2, line 11 * * page 11, line 1 - line 20 * * page 11, line 5 - line 6 * * page 17, line 27 * -----	1-6	INV. A61K9/70 A61K35/02
A	WO 99/15210 A (NOVEN PHARMACEUTICALS, INC; MANTELLE, JUAN; HOUZE, DAVID; KANIOS, DAVI) 1 April 1999 (1999-04-01) * page 4, line 21 - line 36 * * page 8 - page 10 * * page 36, line 31 * * page 67, line 11 - line 14 * * example 1 * -----	1-6	
A	GB 139 077 A (EDMUND MORSE POND) 26 February 1920 (1920-02-26) * page 1, line 4 - line 15 * * page 2, line 25 - line 38 * * page 4, line 4 * -----	1-6	TECHNICAL FIELDS SEARCHED (IPC) A61K
A	US 6 469 227 B1 (COOKE DEDE ET AL) 22 October 2002 (2002-10-22) * column 1 - column 7 * * column 4, line 48 - line 55 * * column 7 *	1-6	
X	US 6 251 423 B1 (BRADFORD COLIN RAYMOND) 26 June 2001 (2001-06-26) * column 1, line 1 - line 15 * * column 2, line 24 - line 26 * * column 4, line 49 - line 58 * * table 1 * ----- -/--	1-6	
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 11 April 2008	Examiner Schüle, Stefanie
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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EUROPEAN SEARCH REPORT

Application Number
EP 07 11 8333

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2004/143026 A1 (SHAH KISHORE R) 22 July 2004 (2004-07-22) * page 1, paragraph 2 * * page 4, paragraph 32 * -----	1-6	
A	US 5 973 010 A (CRAWFORD ET AL) 26 October 1999 (1999-10-26) * column 1 * -----	1-6	
X	GB 2 165 453 A (ROEHM GMBH ROEHM GMBH [DE]) 16 April 1986 (1986-04-16) * page 1, line 110 - line 121 * * page 2 * * page 3, line 30 - line 54 * * examples 1,3 * * claims 1,19 * -----	1,2	
A	US 4 788 061 A (SHORE RONALD N [US]) 29 November 1988 (1988-11-29) * claims 6,7,12 * -----	1-6	
			TECHNICAL FIELDS SEARCHED (IPC)
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 11 April 2008	Examiner Schüle, Stefanie
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EPO FORM 1503 (3.82) (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 11 8333

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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11-04-2008

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0102479	A	11-01-2001	AU 4798300 A	22-01-2001
			CN 1364182 A	14-08-2002

WO 9915210	A	01-04-1999	NONE	

GB 139077	A	26-02-1920	NONE	

US 6469227	B1	22-10-2002	WO 0141746 A1	14-06-2001

US 6251423	B1	26-06-2001	AU 716244 B2	24-02-2000
			AU 5772696 A	29-11-1996
			CA 2217852 A1	21-11-1996
			EP 0827394 A1	11-03-1998
			WO 9636315 A1	21-11-1996
			NZ 308172 A	29-03-1999
			ZA 9603985 A	25-11-1996

US 2004143026	A1	22-07-2004	NONE	

US 5973010	A	26-10-1999	NONE	

GB 2165453	A	16-04-1986	BE 903471 A1	17-02-1986
			CH 667013 A5	15-09-1988
			DE 3438005 A1	17-04-1986
			DK 473885 A	18-04-1986
			FR 2571619 A1	18-04-1986
			IT 1185827 B	18-11-1987
			NL 8502842 A	16-05-1986
			SE 461251 B	29-01-1990
			SE 8504796 A	18-04-1986

US 4788061	A	29-11-1988	CA 1306195 C	11-08-1992

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82